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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/452,843	05/30/95	SETTE	A	014137-00802

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EXAMINER	
DIBRINO, M	
ART UNIT	**PAPER NUMBER**
1644	36

DATE MAILED: 08/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/452,843	Sette et al
Examiner	**Art Unit**
Marianne DiBrino	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on Apr 30, 2001

2a) [X] This action is **FINAL.** 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) 166-175 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) 166-175 is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirem

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved.

12) [X] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) [ ] Notice of References Cited (PTO-892)

16) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) [ ] Interview Summary (PTO-413) Paper No(s). _____

19) [ ] Notice of Informal Patent Application (PTO-152)

20) [ ] Other:

DETAILED ACTION

1. Applicants' amendment filed 4/30/01 (Paper No. 34) is acknowledged and has been entered.

Claims 166-175 are pending.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant is required to provide SEQ ID NO for the sequences listed in the Figures. Applicant is further required to list priority data in section (1)(vii).

Applicant's comments on page 2 of Applicant's said amendment under "Formal Objections" that a submission in compliance with 37 C.F.R. 1.821-1.825 is mailed under separate cover is noted by the Examiner; however, the said submission has not been received and the objection therefore stands as enunciated above.

3. Applicants are required to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, in the Brief Description of the Drawings for Figures 1 and 2). 37 CFR 1.821(The oath or declaration is defective.

4. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: a post office address was not provided for the second inventor.

5. Claims 166-175 are presently being examined.

The following are new grounds of rejection necessitated by Applicant's amendment filed 4/30/01.

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 166-175 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

This rejection is a new matter rejection.

The added material which is not supported by the original disclosure is as follows:

(1) "an immunogenic peptide consisting of about 8-11 amino acid residues that induces a cytotoxic T cell response restricted by at least three alleles selected from the group consisting of B0701, B1401, B3501, B3503, B51-1, B5301, B5401, Cw0602" which consists of or comprises "a subsequence of 8-11 amino acid residues which sequence comprises a first anchor residue at position two of said subsequence which is P, and a second anchor residue at the carboxy terminus of said subsequence selected from the group consisting of V, I, L, F, M, W, Y and A".

Applicant points to support for the position 2 and carboxy-terminal hydrophobic amino acid residue motif in Table 6 on page 33 of application serial no. 08/344,824 and 08/278,634; however, Table 6 discloses carboxy-terminal anchor residues of motifs for the following HLA molecules recited in instant claims 166 and 171 are as follows: for HLA-B0701, LIV(YFW), for HLA-B1401, LIV, for HLA-B3501, no motif is disclosed, for HLA-B3503, FY, for HLA-B5101, LIV, for HLA-B5301, LIVFMYFW, for HLA-B5401, no motif is disclosed, for HLA-Cw0602, LIVMYFW. The recited "motif" for the recited HLA molecule in instant claims 166 and 171 are therefore not supported by the disclosure at Table 6. Applicant also points to support for the motif on page 3 of the instant specification at lines 19-21; however, the specification discloses that "motif" refers to the pattern of residues in a peptide of defined length, usually about 8 to about 11 amino acids, which is recognized by a particular MHC allele. " There is no disclosure of a peptide of about 8-11 amino acid residues which has the specified motif, and there is no disclosure as to whether the motif of position two is at position two of an 8-mer peptide and the carboxy-terminus of an 8-mer peptide or at position 2 of an 11-mer peptide and the carboxy-terminus of an 11-mer peptide.

(2) "one or more fragments of said antigen of interest that consist essentially of said located subsequence" recited in instant claims 166 and 171.

(3) "testing in vitro the ability of said one or more fragments to bind to a first HLA molecule selected from the group set forth above with an IC50 less than 500 nM" recited in instant claim 171. Applicant does not point to support in the disclosure.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 166-175 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

> Claims 166 and 171 are indefinite in the recitation of "B0701, B1401, B3501, B3503, B5101, B5301, B5401, Cw0602" because it is not clear what type of alleles these are, i.e., if they are HLA alleles.

10. With regard to application of prior art, the filing date of the instant claims is that of the instant application, i.e., 5/30/95, because the scope of the claimed invention is not disclosed in parent application 08/344,824, nor in parent application 08/278,634. The parent application does not support the claimed method; in minimis, the parent application does not disclose a method for identifying "an immunogenic peptide consisting of about 8-11 amino acid residues that induces a cytotoxic T cell response restricted by at least three alleles selected from the group consisting of B0701, B1401, B3501, B3503, B51-1, B5301, B5401, Cw0602" which consists of or comprises "a subsequence of 8-11 amino acid residues which sequence comprises a first anchor residue at position two of said subsequence which is P, and a second anchor residue at the carboxy terminus of said subsequence selected from the group consisting of V, I, L, F, M, W, Y and A", and said parent applications do not disclose the elected species APAPAPSWPL.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 166-175 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zakut-Houri et al (EMBO J. 4(5), 1985, pages 1251-1255), Harlow et al (Molec. Cell. Biol., 5(7), 1985, pages 1601-1610) Harris et al (Mol Cell Biol., 6(12), 1986, pages 4650-4656) or Lamb et al (Molec. Cell. Biol., 6(5), 1986, pages 1379-1385) each in view of Hill et al (Nature 360(3), 1992, pages 434-439), Falk et al (Immunogenetics, Vol. 38, 1993, pages 161-162, Applicant's IDS reference), Huczko et al (J. Immunol., 151(5), 1993, pages 2572-2587, Applicant's IDS reference) and Sette et al (J. Immunol. 153: 5586, 1994).

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al teach the amino acid sequence of the human tumor antigen p53.

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al do not teach a method for making an immunogenic peptide comprising APAPAPSWPL.

Falk et al teach that peptides that are T cell epitopes for HLA-B35 have a position 2 Pro and a Leu at the carboxy terminus (especially page 161, column 2 at lines 1-6 of the first full paragraph and page 162, Table 1a).

Hill et al teach that peptides that are T cell epitopes for HLA-B35 have a position 2 Pro and a Leu at the carboxy terminus. Hill et al teach searching sequences of known antigens for potential epitopes based upon motif amino acids and synthesis of said potential epitopes, e.g., peptides of 8-10 amino acid residues in length (especially column 2 on page 434, last paragraph and Table 2, tr15 and tr20). Hill et al also teach peptides that bind to HLA-B51 have position 2 Pro and Val or Ile at the carboxy terminus (especially Figure 1a, peptides cp6, Is6 and sh1, and Table 2) and that these peptides also bind to HLA-B53.

Huczko et al teach that peptides that bind to HLA-B7 have Pro at position 2 and L at the carboxy terminus.

Sette et al teach that an affinity threshold of approximately 500 nM (preferably 50nM or less) apparently determines the capacity of a peptide epitope to elicit a CTL response.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have scanned the p53 tumor antigen amino acid sequence of Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al for subsequences such as APAPAPSWPL that possess the motifs, such as those of Hill et al and Huczko et al, for binding to a HLA class I allele expressed in populations of humans, including HLA-B35 and HLA-B7, to have made the said subsequences in a length compatible with binding to HLA class I molecules (i.e., generally 8-11 amino acid residues in length) residues that are capable of being processed to the appropriate size for presentation by class I, to have tested the affinity of the subsequences for affinity of binding to HLA as taught by Sette et al, and to have tested complexes of the peptide/HLA molecules for their ability to be recognized by CTL restricted by said HLA

molecules. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have tested APAPAPSWPL for binding to HLA-B51 and HLA-B53 because Leu at position 9 of APAPAPSWPL is very similar to Ile of the peptides that bind to HLA-B51 and HLA-B53, and the peptide possesses the position 2 Pro anchor amino acid residue that is common to peptides that bind to HLA-B51, HLA-B53, HLA-B7 and HLA-B35.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce peptides which are potential CTL epitopes for use in vaccines ex vivo or in vivo.

Instant claims 166 and 171 are included because it would have been obvious to prepare and include two or more antigenic peptide "fragments" in a vaccine in order to make a more effective vaccine and because Hill et al teach binding of peptides to more than one HLA allele.

Applicant's comments in the amendment filed 4/30/01 have been fully considered but are not persuasive.

It is Applicant's position, on page 8 of the said amendment at paragraph 1, that Sette et al is not citable with respect to claims 166-168 and 171-173 since these claims are entitled to priority of July 21, 1994, and further that Sette et al was published in 1995 and is the work of the present inventors and that the remaining individuals listed as authors did not contribute to the concept of the present invention. Applicant cites *in re Katz*, 687 F2d 450, 215 USPQ 14 (CCPA 1982). It is Applicant's further position that there is no suggestion in Hill et al, Huczko et al or Sette et al that the method would yield a peptide which would be likely to elicit an immune response in individuals possessing any of a number of different HLA alleles and that Hill et al and Huczko et al teach individual peptides which are associated with binding to a single HLA molecule.

It is the Examiner's position that the instant claims are entitled to the filing date of the instant application as explained supra, i.e., 5/30/95, and that the said Sette et al article was published in 1994. With regard to Applicant's comment on *in re Katz*, it is the Examiner's position that a declaration under 1.132 in accordance with *in re Katz* has not been submitted. It is the Examiner's position that Hill et al teach peptides that bind to more than one HLA allele.

13. Claims 166-175 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zakut-Houri et al (EMBO J. 4(5), 1985, pages 1251-1255), Harlow et al (Molec. Cell. Biol., 5(7), 1985, pages 1601-1610) Harris et al (Mol Cell Biol., 6(12), 1986, pages 4650-4656) or Lamb et al (Molec. Cell. Biol., 6(5), 1986, pages 1379-1385) each in view of Sidney et al (J. Immunol. 154, January 1, 1995, pages 247-259).

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al teach the amino acid sequence of the human tumor antigen p53.

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al do not teach a method for making an immunogenic peptide comprising APAPAPSWPL.

Sidney et al teach peptides with HLA-B7-like supermotif, i.e., Pro at position 2 and hydrophobic/aromatic amino acid residues at the C terminus (especially abstract). Sidney et al teach that the said peptides bind to multiple class I HLA alleles such as HLA-B701, HLA-B5101, HLA-B5301 and HLA-B3501 (especially Table III). Sidney et al teach peptide-based immunizations for the treatment of viral or parasitic infections and cancers and that elicitation of specific class I restricted CTL responses may be crucial in controlling tumor growth and/or prevention of metastasis (especially paragraph spanning pages 247 and 248). Sidney et al further teach that discovery of peptide epitopes capable of broad cross-reactivity among most or all members of the B7-like supertype family of alleles could be of significant practical importance in the development of peptide-based vaccination strategies (especially last paragraph on page 248 before Materials and Methods section). Sidney et al also teach production of synthetic peptides. Sidney et al teach that good binding is equivalent to an IC50 of less than 500 nM (especially line 8 of column 1 on page 252).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have scanned the tumor antigen p53 amino acid sequence of Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al for subsequences, including APAPAPSWPL, which comprise a binding motif for any of the HLA alleles, including HLA-B701, HLA-B5101, HLA-B5301 and HLA-B3501, which have the B7-like supermotif of Sidney et al, including Pro at position 2 and Leu at the carboxy terminus, to make the said subsequences in a length compatible with binding to HLA class I molecules (i.e., generally 8-10 or 11 amino acid residues in length), to complex said subsequences with the class I HLA molecules, to determine affinity, to select peptides with an affinity of less than 500 nM and to test for CTL responses to said peptides when in complex with HLA class I molecules.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to provide peptides for vaccines as taught by Sidney et al.

Instant claims 166 and 171 are included because it would have been obvious to prepare and include two or more antigenic peptide "fragments" in a vaccine in order to make a more effective vaccine.

Applicant's comments in the amendment filed 4/30/01 have been fully considered but are not persuasive.

It is Applicant's position, on page 8 of the said amendment at paragraph 3, that Sette et al is not citable with respect to claims 166-168 and 171-173 since these claims are entitled to priority of July 21, 1994, and further that Sette et al was published in 1995 and is the work of the present inventors and that the remaining individuals listed as authors did not contribute to the concept of the present invention. Applicant cites *in re Katz*, 687 F2d 450, 215 USPQ 14 (CCPA 1982).

It is the Examiner's position that the instant claims are entitled to the filing date of the instant application as explained supra, i.e., 5/30/95, and that the said Sette et al article was published in 1994. With regard to Applicant's comment on *in re Katz*, it is the Examiner's position that a declaration under 1.132 in accordance with *in re Katz* has not been submitted.

14. Claims 166-175 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Zakut-Houri et al (EMBO J. 4(5), 1985, pages 1251-1255), Harlow et al (Molec. Cell. Biol., 5(7), 1985, pages 1601-1610) Harris et al (Mol Cell Biol., 6(12), 1986, pages 4650-4656) or Lamb et al (Molec. Cell. Biol., 6(5), 1986, pages 1379-1385) each in view of Hill et al (Nature 360(3), 1993, pages 434-439), and Huczko et al (J. Immunol., 151(5), 1993, pages 2572-2587, Applicant's IDS reference)

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al teach the amino acid sequence of the human tumor antigen p53.

Zakut-Houri et al, Harlow et al, Harris et al or Lamb et al do not teach a method for making an immunogenic peptide comprising APAPAPSWPL.

Hill et al teach that peptides that are T cell epitopes for HLA-B35 have a position 2 Pro and a Leu at the carboxy terminus. Hill et al teach searching sequences of known antigens for potential epitopes based upon motif amino acids and synthesis of said potential epitopes, e.g., peptides of 8-10 amino acid residues in length (especially column 2 on page 434, last paragraph and Table 2, tr15 and tr20). Hill et al also teach peptides that bind to HLA-B51 have position 2 Pro and Val or Ile at the carboxy terminus (especially Figure 1a, peptides cp6, Is6 and sh1, and Table 2) and that these peptides also bind to HLA-B53.

Huczko et al teach that peptides that bind to HLA-B7 have Pro at position 2 and L at the carboxy terminus.

It is the Examiner's position that the instant claims are entitled to the filing date of the instant application as explained supra, i.e., 5/30/95, and that the said Sette et al article was published in 1994. With regard to Applicant's comment on *in re Katz*, it is the Examiner's position that a declaration under 1.132 in accordance with *in re Katz* has not been submitted. It is the Examiner's position that Hill et al teach peptides that bind to more than one HLA allele.

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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